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Original Scientific Paper

THE PREDICTIVE ROLE OF LEPTIN IN MALNUTRITION-INFLAMMATION COMPLEX SYNDROME IN HEMODIALYSIS PATIENTS

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SUMMARY – Leptin is a protein hormone secreted by adipocytes. Its role in malnutrition-inflammation complex syndrome (MICS) in hemodialysis (HD) patients has not been fully resolved yet. We aimed to assess the predictive role of serum leptin in MICS in maintenance HD patients. This prospective study included 93 HD patients who were distributed in three groups according to serum leptin levels (low-normal-high). Nutritional and inflammatory parameters of MICS, as well as malnutrition-inflammation score (MIS), were determined at baseline and after 12 months. In all subjects, the median serum leptin levels were above the relevant reference range at both the baseline (10 ng/mL; interquartile range (IQR) 4.2-29.9 ng/mL) and at the 12-month follow-up (13 ng/mL; IQR 3.5-39.5 ng/mL). Patients with decreased serum leptin levels had elements of MICS present. Leptin exhibited good sensitivity (0.89), while its specificity was similar to that of other nutritional and inflammatory parameters (0.45 for leptin *vs.* 0.65 for body mass index, 0.46 for MIS, 0.63 for C-reactive protein, 0.44 for albumins, 0.47 for ferritin and 0.50 for transferrin). The ROC curve analysis identified leptin levels of ≤3.4 ng/mL in men and ≤11.4 ng/mL in women to have the best predictive value for MICS. In conclusion, leptin appears to be a reliable marker of MICS.

Key words: *Leptin; Malnutrition-inflammation complex syndrome; Hemodialysis*

Introduction

Leptin is a protein hormone consisting of 167 amino acid residues in four spiral chains. It is predominantly synthesized in white adipose tissue, as a product of the obesity *(ob)* gene. Its name derives from the Greek word for lean, *leptos*[1,2]. Leptin plays a major role in the regulation of food intake and energy consumption[3]. Furthermore, it influences several physiological processes, including glucose, lipid and bone metabolism, hematopoiesis, immune, reproductive and cardiovascular functions[1,4]. Women have greater leptin values in circulation compared to men. This is explained by the adverse effects of androgen and the positive effect of estrogen on leptin synthesis[1,2]. Leptin synthesis is affected by several factors. Starvation, physical activity, exposure to

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cold, noradrenalin, and activation of beta-adrenergic receptors in adipose tissue all reduce leptin synthesis[3,5-7]. Food intake, obesity, emotional stress, glucose, insulin, triiodothyronine, and dexamethasone increase leptin synthesis[3,8,9].

Malnutrition-inflammation complex syndrome (MICS) has been associated with morbidity and poor outcomes in hemodialysis (HD) patients[10]. Its prevalence in this population ranges from 30% to 60%[11]. The syndrome is characterized by coexisting chronic inflammation and protein-energy malnutrition[12,13]. Various causes have been identified for this syndrome, e.g., anorexia, restrictive diets to balance serum calcium and phosphate, protein hypercatabolism, protein loss *via* dialysis, infections, endocrine disorders, metabolic acidosis, and other comorbidities[12]. There is currently no single universal test to diagnose the presence of MICS[14]. Due to the complexity of this phenomenon, many procedures are involved in its evaluation, including anthropometric measurements, biochemical analyses, scores, assessment of functional status, and dietary habits. The sensitivity and specificity of certain biochemical variables in identifying the state of malnutrition and inflammation have not yet been fully recognized[14-16].

Previous studies have reported on the association between leptin and the development of anorexia and malnutrition in uremic patients, but its role in malnutrition progression and its clinical significance within MICS have not yet been established[17,18]. Some studies hypothesized that chronic kidney disease (CKD) patients might have an acquired leptin receptor disorder, similar to leptin resistance seen in obese persons[18,19]. Elevated leptin levels accompany parameters of adequate nutritional status, such as serum albumin, prealbumin, total cholesterol, and low malnutrition-inflammation score (MIS), thus implying that leptin mirrors alterations in body composition occurring within MICS[17,20,21]. Leptin is influenced by hypervolemia and acidosis, i.e., factors which influence other laboratory parameters used in MICS assessment[22].

In this study, we aimed to assess the predictive role of leptin in MICS in patients on maintenance HD.

Materials and Methods

This prospective study included 93 patients with chronic HD treated at the International Dialysis Center in Laktaši, Bosnia and Herzegovina, followed-up for 12 months, from January 2019 until January 2020. The subjects were distributed in three groups according to serum leptin levels as follows: low (≤0.34 ng/mL for males; ≤2.42 ng/mL for females), normal (0.35-9.61 ng/mL for males; 2.43-28 ng/mL for females), and high (≥9.63 ng/mL for males; ≥29 ng/mL for females) levels. The study protocol was approved by the institutional Ethics Committee. Written informed consents were obtained from all participants before the study procedures.

All patients were dialyzed on machines with controlled ultrafiltration, using high-flux Cor-Diax membranes, 3 times *per* week for 4 hours. Dialysis adequacy was assessed with the index of the removal efficiency *per* dialysis session (Kt/V), online clearance monitoring module, and urea reduction ratio. The underlying renal diseases were chronic pyelonephritis (27.95%), diabetic nephropathy (22.6%), glomerulonephritis (14%), cystic renal disease (11.8%), renovascular disease (6.45%), or other renal diseases (17.2%). Exclusion criteria were less than 3-month dialysis vintage, less than 3 weekly HD sessions, corticosteroid treatment, and/or thyroid dysfunction[3,7,9].

Biochemical analyses were performed at baseline and after 12 months. Predialysis blood samples were collected upon a midweek dialysis session. The following parameters were measured: leptin, hemoglobin, creatinine, albumin, total cholesterol, transferrin, ferritin, and C-reactive protein (CRP). Serum leptin was determined by the human enzyme-linked immunosorbent assay (ELISA) kit manufactured by BioVendor, with a reference range of 0.35-9.61 ng/mL for men and 2.43-28 ng/mL for women. Creatinine was determined with Jaffe's kinetic reaction, serum albumin by spectrophotometry, total cholesterol by enzymatic colorimetric test, CRP and transferrin by turbidimetric method, and ferritin by immuno-chemiluminescent method on an AU 680 Olympus analyzer. Body mass index (BMI) was calculated with the Quetelet equation, as the body mass (in kg) divided by the square of the body height (in m^2).

The Malnutrition Inflammation Score (MIS) was used to assess the presence of MICS. MIS has ten components in four sections (nutritional history, physical examination, BMI, and laboratory values), each with four levels of severity, from 0 (normal) to 3 (very severe). The sum of all 10 MIS components

ranges from 0 to 30, in which a higher score reflects a more severe degree of malnutrition and inflammation[7]. In our study, the cut-off value for MIS which defined the presence of MICS was 6.

Statistical methods

The normality of the distribution of datasets was assessed with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean with standard deviation (SD). Non-normal variables were reported as median with interquartile range (IQR). We used the Student's t-test for unpaired samples or an ANOVA test for multiple unpaired samples to compare the means between continuous variables with normal distribution, and a nonparametric Mann-Whitney test for unpaired samples or non-parametric Kruskal-Wallis test for multiple unpaired samples if the observed features did not have normal distribution. When using the Student's t-test, the significance of variations of the observed features was tested with the F test. The non-parametric Friedman test was used for comparing more than two data sets with non-normal distribution. Binary logistic regression was used to assess the sensitivity and specificity of leptin, anthropometric and laboratory tests in predicting MICS, as presented with the receiver operating curve (ROC). All analyses were performed using the IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic, clinical, and laboratory parameters are presented in Tables 1 and 2. There were 93 patients

Table 1. Demographic, clinical, and laboratory parameters of dialysis patients according to serum leptin levels at baseline

Variable	Low leptin level	Normal leptin level	High leptin level	All	p
n	9	43	41	93	
Age (years)	66.73±11.64[a]	62.60±13.62[b]	66.22±18.32[a]	64.30±13.20	<0.05
Dialysis vintage (months)	93.55±56.19[a]	88.46±55.72[b]	78.90±71.2[c]	84.72±62.7	<0.001
BMI (kg/m^2)	19.09±1.24[a]	22.83±2.72[a]	27.92±3.80[b]	23.28±2.58	<0.001
Hemoglobin (g/L)	106.56±14.09[a]	110.93±14.93[a]	115.63±9.58[b]	112.58±12.96	<0.05
Albumin (g/L)	36.36±3.42[a]	41.02±2.78[b]	41.66±3.11[b]	40.85±3.32	<0.001
Creatinine (μmol/L)	599.00±90.33[a]	740.93±138.51[b]	744.39±145.20[b]	728.72±143.04	<0.05
Cholesterol (mmol/L)	3.75±0.71[a]	4.35±1.10[b]	4.99±0.98[b]	4.57±1.09	<0.001
CRP (mg/L)	10.13±6.45[a]	7.88±11.59[b]	6.94±8.14[b]	7.68±9.73	<0.001
Ferritin (ng/mL)	865.22±407.89[a]	490.88±277.06[b]	424.00±283.12[b]	593.95±306.12	<0.001
Transferrin (g/L)	1.26±0.29[a]	1.58±0.38[b]	1.64±0.27[b]	1.58±0.34	<0.05
MIS	11.11±1.69[a]	4.78±1.31[b]	3.87±1.45[b]	5.04±2.48	<0.001
Kt/v	1.50±0.18[a]	1.49±0.22[a]	1.49±0.21[a]	1.49±0.20	ns
OCM	1.62±0.23[a]	1.60±0.20[a]	1.59±0.18[a]	1.60±0.20	ns
URR (%)	75.11±4.37[a]	74.44±5.89[a]	73.61±6.98[a]	74.38±5.74	ns
RD (mL/24 h)	185.14±12.15[a]	275.10±18.65[b]	267.11±25.92[b]	242.45±18.90	<0.05

Data are presented as mean ± SD; n = number of patients, BMI = body mass index; MIS = malnutrition inflammation score; Kt/V = index of removal efficiency *per* dialysis session; OCM = online clearance monitoring; URR = urea reduction ratio; RD = residual diuresis; [a,b,c]differences among groups with low, normal and high serum leptin levels, significant difference present between values with different markings (p<0.05); ns = nonsignificant

Table 2. Demographic, clinical, and laboratory parameters of dialysis patients according to serum leptin levels at the end of the follow-up

Variable	Low leptin level	Normal leptin level	High leptin level	All	p
n	9	36	38	83	
Age (years)	69.66±10.66[a]	59.97±14.82[b]	67.18±10.94[a]	64.32±13.19	<0.001
Dialysis vintage (months)	103.33±48.77[a]	99.35±74.14[b]	82.65±54.95[c]	96.06±63.97	<0.001
BMI, (kg/m^2)	20.08±2.71[a]	22.47±2.66[a]	27.11±4.16[b]	24.83±4.32	<0.001
Hemoglobin (g/L)	106.78±12.26[a]	116.31±9.35[b]	116.58±8.87[b]	113.40±9.83	<0.05
Albumin (g/L)	38.72±7.91[a]	42.97±3.85[a]	42.37±2.87[a]	42.23±4.21	ns
Creatinine (μmol/L)	623.00±135.5[a]	759.79±128.6[b]	764.49±150.3[b]	745.67±142.3	<0.05
Cholesterol (mmol/L)	4.06±1.46[a]	4.48±1.30[a]	5.03±1.19[a]	4.68±1.30	ns
CRP (mg/L)	13.28±16.71[a]	7.69±11.35[b]	9.64±10.83[b]	9.19±11.75	<0.001
Ferritin, (ng/mL)	818.33±628.88[a]	448.92±297.49[b]	461.82±323.13[b]	575.66±360.92	<0.001
Transferrin (g/L)	1.54±0.41[a]	1.68±0.37[a]	1.68±0.43[a]	1.66±0.37	ns
MIS	11.89±2.47[a]	4.89±1.69[b]	3.88±1.30[b]	5.54±2.90	<0.001
Kt/v	1.43±0.26[a]	1.41±0.22[a]	1.41±0.35[a]	1.41±0.27	ns
OCM	1.65±0.26[a]	1.63±0.23[a]	1.61±0.18[a]	1.63±0.22	ns
URR (%)	73.82±6.29[a]	73.71±4.55[a]	72.79±5.73[a]	73.44±5.52	ns
RD (ml/24h)	179.29±35.16[a]	260.11±25.14[b]	263.58±39.68[b]	234.32±33.32	<0.05

Data are presented as mean ± SD; n = number of patients; BMI = body mass index; MIS = malnutrition inflammation score; Kt/V = index of removal efficiency *per* dialysis session; OCM = online clearance monitoring; URR = urea reduction ratio; RD = residual diuresis; [a,b,c]differences among groups with low, normal and high serum leptin levels, significant difference present between values with different markings (p<0.05); ns = nonsignificant

enrolled at baseline, 59% of men and 41% of women, mean age 64.3±13.2 years, and mean dialysis vintage 84.7±62.7 months. At the end of the follow-up, 83 patients were alive, 9 dead, and 1 underwent kidney transplantation. The median leptin value was 10 ng/mL (IQR 4.2-29.9) at baseline, and 13 ng/mL (IQR 3.5-39.5) at the end of the follow-up. The mean MIS was 5.04±2.48 at baseline, and 5.54±2.90 after 12 months (Tables 1 and 2).

Patients with low serum leptin levels were significantly older and had significantly longer dialysis vintage than patients with normal or high serum leptin (Table 1). Hemoglobin and creatinine levels were significantly lower (p<0.05), while CRP, ferritin, and MIS were significantly higher (p<0.001) in patients with low serum leptin at both baseline and at the end of the follow-up, compared to patients with normal or high leptin (Tables 1 and 2). Serum cholesterol, transferrin (p<0.05), and albumin (p<0.001) were significantly lower at baseline in patients with low serum leptin compared to the other two groups (Table 1). However, at the end of the follow-up, there were no significant differences between the groups concerning these three parameters. BMI was lower in patients with low and normal serum leptin levels than in patients with high serum leptin levels both at baseline and at the end of the follow-up (Tables 1 and 2). Patients with low serum leptin had lower residual diuresis than

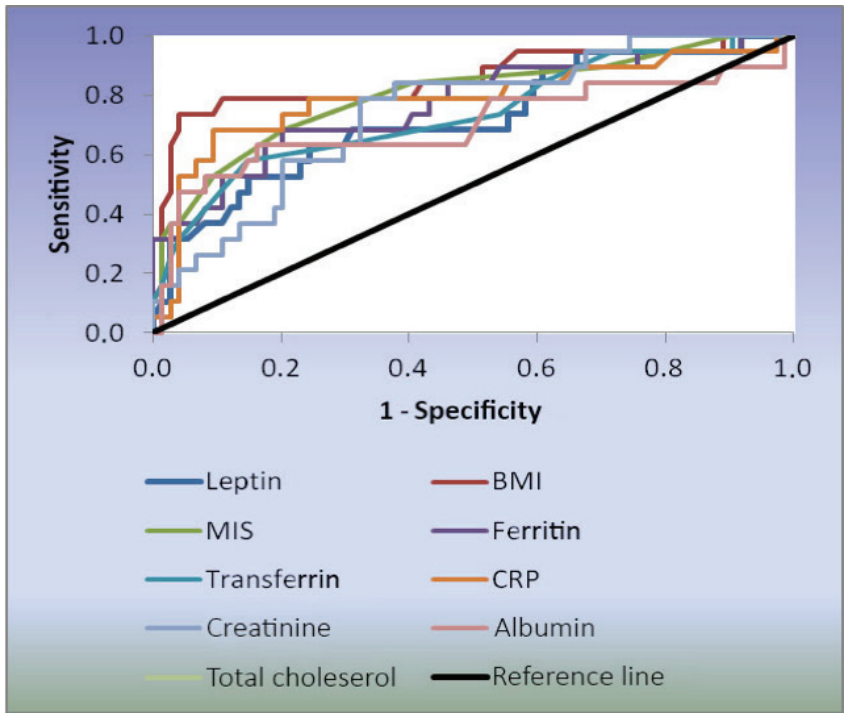

Fig. 1. Sensitivity and specificity of serum leptin and other parameters in predicting malnutrition-inflammation complex syndrome according to ROC curve (the area under curve for leptin 0.77, p<0.003, BMI 0.857, p<0.001; MIS 0.799, p<0.001; ferritin 0.769, p<0.001; transferrin 0.737, p=0.001; CRP 0.788, p<0.001; albumin 0.702, p<0.007, and total cholesterol 0.543, p=0.564).

patients in the other two groups at baseline and at the end of the study (Tables 1 and 2).

When considering sex-related differences, women had adequate albumin levels regardless of the serum leptin levels (42.3±4.56 *vs.* 42.4±5.69 *vs.* 43.33±3.55 g/L), while men with low serum leptin levels also had significantly lower albumin levels compared to women (36.4±2.35 *vs.* 42.4±0.89 *vs.* 43.1±5.36 g/L, p<0.05). Women had a higher MIS than men in all study groups, both at baseline (11.50±2.08 *vs.* 5.00±1.69 *vs.* 3.61±1.68 women; 10.80±1.48 *vs.* 4.82±1.19 *vs.* 4.15±1.13 men) and at the end of the follow-up (17.02±2.56 *vs.* 4.76±0.56 *vs.* 4.14±2.11 women; 12.16±5.23 *vs.* 4.61±1.21 *vs.* 3.73±1.56 men). Women with low serum leptin levels had significantly higher MIS at the end of the follow-up (p<0.001). Low serum leptin levels were associated with significantly higher MIS in women at the end of the study (p<0.001), while men with low serum leptin levels had significantly lower albumin levels compared to women (p<0.05). No significant sex-related differences were found in other examined parameters.

Body mass index exhibited highest sensitivity and specificity in predicting MICS, followed by CRP and MIS. Total cholesterol had lowest sensitivity and specificity in predicting MICS. Leptin showed good sensitivity (0.89), while its specificity was similar to that of other parameters (0.45 for leptin, 0.65 for BMI, 0.46 for MIS, 0.63 for CRP, 0.44 for albumin, 0.48 for ferritin, and 0.50 for transferrin), as shown in Figure 1.

The optimal cut-off points of serum leptin levels for predicting MICS in the forthcoming 12 months were ≤3.4 ng/mL in men and 11.4 ng/mL in women, as determined with the ROC curve analysis. At the beginning of the study, 38 subjects, 20 women and 18 men (40.86%) had lower values than these, and at the end of the study, the same was true for 30 subjects, 16 women and 14 men (36.14%).

Discussion

The syndrome of malnutrition and inflammation is associated with erythropoietin hyporesponsiveness, a high rate of cardiovascular atherosclerotic disease,

decreased quality of life, and increased morbidity and mortality in dialysis patients[12,14]. Numerous conditions have been associated with the development of MICS, including certain comorbidities, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and a low nutrient intake, uremic toxins, decreased clearance of the inflammatory cytokines, volume overload, and dialysis-related factors[10,13-16]. Previous research has not yet defined the exact roles of certain mediators, leptin being one of them, in predicting MICS. Catabolic processes within MICS are accompanied by alterations of serum leptin levels, but the nature, reliability, and sensitivity of this association have not yet been established[19,24,25]. Leptin is involved in the regulation of appetite and might have a role in the development of anorexia in uremic patients through inflammation-related suppression of appetite[19,26,27]. Therefore, considering the sex-related differences in the reference values for serum leptin, we aimed to further explore this relationship.

Leptin levels in CKD and end-stage renal disease patients are usually significantly elevated, probably related to decreased renal clearance of this substance[22,26]. Still, the presence of either increased or decreased leptin levels in these patients suggests that other factors may also play a significant role in this matter. Differences in the reference levels of leptin in men and women are explained by the negative impact of androgens and positive effect of estrogen on leptin synthesis. In patients on chronic dialysis, other factors may play a role as well, such as dialysis quality, inflammation, drugs, etc.[19,22,23]. During a one-year follow-up period in this study, we did not observe a statistically significant difference in the overall serum leptin levels at the end of the study compared to those at the baseline.

Previous studies have shown that HD vintage was directly correlated with the development of MICS and a significant decrease in leptin. Furthermore, lower leptin levels are associated with worse outcomes in HD[24,28]. Insufficient food intake and increased protein catabolism have also been shown to be related to the aging process, thus elderly patients had a higher prevalence of MICS[12,21]. In our study, longer dialysis duration was associated with older age, MICS, and low serum leptin levels. Changes in leptin levels in the general population were associated with metabolic changes, aging, and nutritional status[2,3]. Our results imply that MICS in elderly patients was associated with lower serum leptin levels.

Furthermore, serum leptin was low in HD patients with lower BMI and serum albumin levels[29,30]. However, patients with serum leptin levels within the reference range had adequate nutritive status and MIS below the cut-off value. In this study, high serum leptin was observed in HD patients with higher BMI, cholesterol, and triglyceride levels. These patients also had adequate nutritive status and MIS below the cut-off value. During the one-year follow-up, the nutritional status of our subjects improved, accompanied by a rise in serum leptin levels. Previous investigations observed that changes in leptin levels mirrored variations in BMI and mid-upper arm circumference, thus suggesting that leptin might indicate malnutrition[32-34]. However, when analyzed by sex, men with low serum leptin levels also had low albumin levels, while all patients with low serum leptin had higher MIS throughout the follow-up period.

Until now, the sensitivity and specificity in the assessment of MICS have been investigated for BMI, CRP, MIS, albumin, and ferritin. Among them, CRP and MIS showed highest sensitivity[11,25]. In our study population, BMI exhibited highest sensitivity and specificity, while total cholesterol showed lowest sensitivity and specificity. The sensitivity and specificity of serum leptin in the assessment of MICS in HD patients have not been addressed previously. Some results show similar sensitivity, but higher specificity of leptin as a malnutrition parameter in the elderly[35]. Both sensitivity and specificity of serum leptin as a nutrition marker were lower in oncologic patients than in our study cohort[36]. Our results showed good sensitivity of serum leptin in MICS assessment compared to other parameters.

Currently, there are no data on the predictive value of serum leptin in the assessment of MICS in HD patients. Data exist on the role of leptin in predicting malnutrition in the elderly[34-36]. The results of our study show that low serum leptin level was associated with MICS. The predictive value of serum leptin in men in our study population was similar to men in the general population.

Conclusions

Our results showed that low serum leptin levels were associated with the presence of MICS in HD patients and that leptin could be considered a reliable parameter of MICS compared to other traditional markers such as BMI, MIS, CRP, ferritin, and transferrin.

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Sažetak

ULOGA LEPTINA U PREDVIĐANJU KOMPLEKSNOG SINDROMA POTHRANJENOSTI I UPALE KOD BOLESNIKA NA KRONIČNOJ HEMODIJALIZI

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Leptin je proteinski hormon koji izlučuju adipociti. Uloga leptina u predviđanju kompleksnog sindroma pothranjenosti i upale (MICS) kod bolesnika na kroničnoj hemodijalizi (HD) još uvijek nije u potpunosti ispitana. Cilj studije bio je ispitati ulogu leptina u predviđanju MICS-a kod bolesnika na kroničnoj HD. Prospektivna studija je obuhvatila 93 bolesnika na HD koji su bili podijeljeni u tri skupine prema razini serumskog leptina. Određivani su prehrambeni i upalni parametri, izračunat je zbroj pothranjenosti i upale (MIS) na početku studije i nakon 12 mjeseci. Srednja razina serumskog leptina bila je povišena tijekom praćenja: 10 ng/mL (IQR 4,2-29,9) na početku, 13 ng/mL (IQR 3,5-39,5) na kraju istraživanja. Bolesnici sa sniženom razinom leptina u serumu imali su MICS. Leptin je pokazao zadovoljavajuću osjetljivost (0.89), a specifičnost je bila slična kao kod drugih prehrambenih i upalnih parametara (0,45 za leptin prema 0,65 za indeks tjelesne mase, 0,46 za MIS, 0,63 za C-reaktivni protein, 0,44 za albumin, 0,47 za feritin i 0,50 za transferin). Analiza krivulje ROC je pokazala da vrijednost serumskog leptina ≤3,4 ng/mL kod muškaraca i 11,4 ng/mL kod žena ukazuje na pisutnost MICS-a. U zaključku, leptin se pokazao pouzdanim parametrom MICS-a.

Ključne riječi: *Leptin; Kompleksni sindrom pothranjenosti i upale; Hemodijaliza*